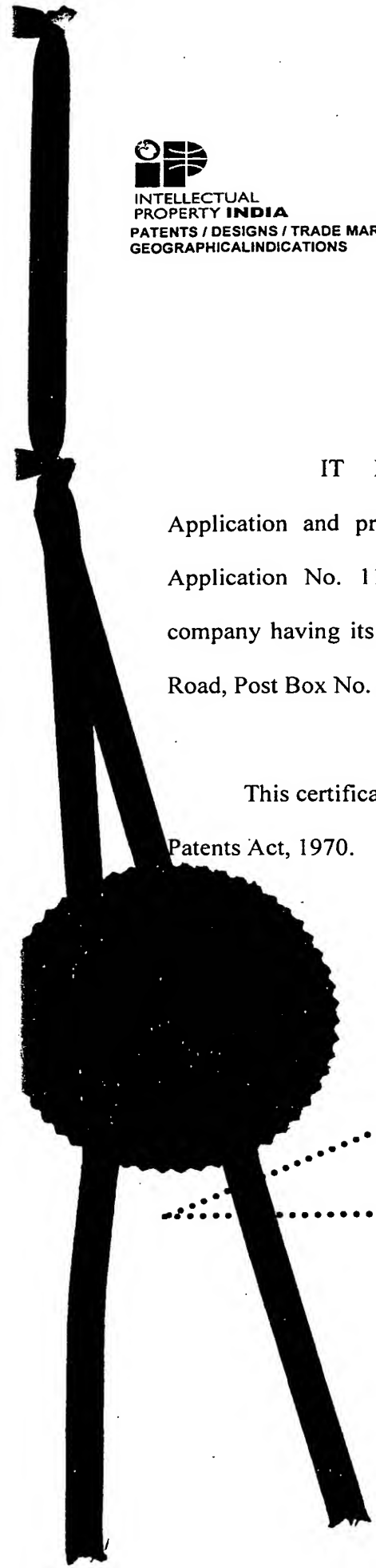

INTELLECTUAL PROPERTY **INDIA**
PATENTS / DESIGNS / TRADE MARKS/ GEOGRAPHICALINDICATIONS

सत्यमेव जयते

Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and provisional specification filed on 12/11/2003 in respect of Patent Application No. 1180/MUM/2003 of Glenmark Pharmaceuticals Limited, an Indian company having its registered office at B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No. 26511, Mumbai – 400 026, India.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

Dated this 26th day of March 2004.

(N.K. GARG)
ASST. CONTROLLER OF PATENTS & DESIGNS.

FORM 1
THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF A PATENT (Section 5(2)7 and Rule 33A)

We, Glenmark Pharmaceuticals Limited, an Indian company having its registered office at B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No.26511 Mumbai – 400 026 INDIA hereby declare

1(a) that we are in possession of an invention titled **"MODIFIED RELEASE FORMULATIONS FOR MANAGEMENT OF SKELETAL MUSCLE SPASMS."**

(b) that the provisional specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

2. further declare that the inventors for the said invention are

(a) **NILENDU SEN, ANANDI KRISHNAN** All citizens & residents of India belonging to Glenmark Pharmaceuticals Limited , B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No.26511 Mumbai – 400 026

(b) **KAVITA CHANDURKAR** citizen of India & resident of Apartment C-301, Janeway Apartment , New Foundland Drive, St John's NL A1A1T1, Canada.

3. that we are the assignee of the true and first inventors

4. that our address for service in India is as follows;

Glenmark Pharmaceuticals Limited
Plot No.A-607, T.T.C Industrial Area
M.I.D.C., Mahape
Navi Mumbai – 400 709
INDIA

5. We, the true and first inventors for this invention declare that the applicant herein is our assignee

(Signed) _____
NILENDU SEN

(Signed) _____
KAVITA CHANDURKAR

(Signed) _____
ANANDI KRISHNAN

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application

7. Following are the attachments with the application
(a) Provisional Specification (23 pages, in duplicate)
(b) Fee Rs. 3000.00 (three thousand rupees only) by Cheque No.054693 dated Oct 29, 2003 & Cheque No.054763 dated Nov 11, 2003 drawn on UTI Bank Ltd

We request that a patent may be granted to us for the said invention

Dated this Eleventh (11th) day of November 2003

CHERYL PINTO
Director
Glenmark Pharmaceuticals Limited

81/MUM-WTO/2003
1180/MUM/2003
dtd. 12/11/2003

To,
The Controller of Patents
The Patents Office Branch, Mumbai

Received Rs. 3000/- in Cash
Cheque/M.O./P.O. on 12/11/03
Vide Entry No. 5526 in the Register of Valuables, Bombay.

FORM 2

THE PATENTS ACT 1970
(Act 39 of 1970)

PROVISIONAL SPECIFICATION

(SECTION 10)

MODIFIED RELEASE FORMULATIONS FOR MANAGEMENT OF SKELETAL MUSCLE SPASMS

Glenmark Pharmaceuticals Limited, an Indian Company,
registered under the Indian company's Act 1957 and
having its registered office at

B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road
Post Box No. 26511
Mumbai - 400 026, India

THE FOLLOWING SPECIFICATION DESCRIBES THE NATURE OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to a hydrophilic controlled release oral formulation containing the muscle relaxant drug tizanidine. The formulation is useful in the treatment of painful and inflammatory conditions associated with skeletal muscle spasms.

BACKGROUND OF THE INVENTION

The present invention relates to a Controlled Release pharmaceutical composition for oral delivery comprising pharmaceutically effective amounts of tizanidine which acts as an alpha adrenoreceptor agonist and is used in the treatment of pain.

Alpha adrenoreceptor agonists play an important role in the treatment of pain. They block nerve impulses. They also act as skeletal muscle relaxants and can be used in combination with certain anti-inflammatory and analgesic drugs to relieve pain and also give a relaxant effect in certain arthritic conditions.

Tizanidine belongs to the class of alpha 2- adrenoreceptor agonists. Tizanidine is a potent centrally acting myotonolytic agent that principally affects spinal polysynaptic reflexes. This action arises from agonistic activity of the compound at noradrenergic alpha 2 receptors, resulting in both direct impairment of excitatory amino acid release from spinal interneurons and a concomitant inhibition of facilitatory coeruleospinal pathways. These findings, together with a possible greater separation between myotonolytic and general CNS depressant activity than with other agents, makes tizanidine a valuable addition in the pharmacologic treatment of spasticity. Tizanidine is available as 2mg and 4mg tablets for oral administration. Tizanidine is administered as an oral dose in tablet form two to three times a day. This kind of therapy has disadvantages, the main side-effect being somnolence. The sedating effects may interfere with everyday activity and presently, patients are warned about performing activities requiring alertness, such as driving a vehicle or operating machinery while taking tizanidine. The effect appears to be dose related.

Zanaflex™ capsules available as comprising of immediate release multiparticulate composition of tizanidine have partially solved this problem by providing a more stable serum level (U.S. PAT. No.6,455,557). However, the disadvantage of frequent dosing leading to reduced patient compliance remains.

A controlled release dosage form of tizanidine will require less frequency of dosing thus improving patient compliance.

A review of the prior art in this context reveals that many patents have been published/issued pertaining to controlled release of alpha agonists either separately or in combination with opioids.

U. S. Patent No. 5,484,607 (Assignee: H. Joseph Horacek, Filed date: Oct 13, 1993, Issued date: Jan 16, 1996) describes controlled release systems for an alpha-agonist: clonidine. The patent describes the method of preparation of an Extended / Sustained Release Matrix dosage form incorporating hydrophilic cellulose ethers as the polymeric agents for extended / sustained release of the active ingredient.

U. S. Patent Application No. 2002044966 (Assignee: Betzing Juergen; Bartholomaeus Johannes, Filed date: July 18, 2001, Publication date: April 18, 2002) discloses a pharmaceutical formulation comprising in combination an opioid and an alpha-agonist wherein at least one of said opioid and alpha-agonist is present in delayed release form. This provides effective pain relieving formulation which lowers the side effects of opioids. The formulation is suitable for treating severe to very severe pain. The composition very considerably delays the development of opioid tolerance. However. there remains a chance to develop a formulation containing a combination of an alpha agonist and a COX-2 inhibitor. This will totally avoid the side effects associated with opioids like gastrointestinal & renal toxicity. A combination therapy will also have adjuvant pain-relieving characteristics & may be beneficial in various cases of neuropathic pain.

US Patent No. 4,515,802: (Assignee: Sandoz Ltd., Filed date: March 8, 1984, Publication date: May 7, 1985) wherein an immediate release formulation containing a combination of an analgesic paracetamol and tizanidine has been claimed.

WO02058620: (Assignee: Osmotica, Costa Rica, Filed date: Jan 25, 2002, Publication date: Aug 01 2002) where the invention relates to a pharmaceutical compositions and dosage forms that combine a COX-II inhibitor and a muscle relaxant in either immediate release and/or extended release forms. The pharmaceutical composition is used to treat pain and symptoms associated with pain. The combination provides an improved therapeutic response compared to all other single drugs.

WO03005951: (Assignee: Teva Pharmaceuticals, Filed date: July 10, 2002, Publication date: January 23 2003) describes a controlled release formulation of a drug in a core, a cylindrical plug embedded in a core and a coating impermeable to the drug. The composition provides zero-order drug release profiles as well as more complicated release profiles. A controlled release formulation of tizanidine in the core along with excipients like microcrystalline cellulose, xylitol, which comprises of the lower layer , an upper layer consisting of placebo constituting sucrose, polyvinyl pyrrolidone & magnesium stearate, a cylindrical plug formed of hydroxy propyl cellulose, methyl cellulose, croscarmellose sodium, magnesium stearate on the upper layer and a coating of ethylcellulose, polyethylene glycol 1000.

A review of the above mentioned patents indicates that there remains a distinct advantage in developing a controlled release formulation of tizanidine that provides once daily dosing for effective management of pain. Also there remains scope for development of such a formulation in combination with a cyclooxygenase inhibitor such as valdecoxib in an immediate release form that provides improved therapeutic response for the treatment of pain related to arthritic conditions.

It is therefore an object of the present invention to provide an orally administrable dosage form that when dosed once daily to humans provides therapeutic relief from pain associated with certain arthritic conditions, by releasing the drug i.e. tizanidine in such a manner that

requisite blood levels are maintained for periods sufficient to justify once a day dosing and thus ensure patient compliance.

It is a further object of the present invention to provide an oral controlled release tablet composition of a muscle relaxant like tizanidine which may also be advantageously combined with an immediate release formulation of a selective COX-2 inhibitor such as valdecoxib.

It is a further object of this invention to discuss various methods suitable for the preparation of an oral controlled release tablet composition of tizanidine which are feasible on industrial scale.

SUMMARY OF THE INVENTION

The present invention directs to an extended release formulation of tizanidine which can be administered orally. The present invention comprises an oral extended release dosage form which releases the drug over an extended period of time. The present invention is proposed to minimize the dose-related side effects while maintaining the efficacy and improving the patient compliance.

Controlled release has been achieved by embedding the drug, tizanidine HCl in a matrix of a suitable hydrophilic polymer. The formulation further contains inactive ingredients such as diluents and lubricants.

The hydrophilic matrix tablet swells as soon as it comes in contact with water. The water then permeates through the swollen matrix and dissolves the drug which then diffuses out of the matrix over a period of 14 -16 hours.

This formulation may also be combined with an anti-inflammatory drug such as valdecoxib in an immediate release fraction.

These and other aspects of the present invention will be better understood with reference to the following description and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention it has been possible to formulate a tablet composition of tizanidine wherein tizanidine is released in a sustained manner using a hydrophilic polymer matrix. The present invention provides a composition giving a plasma-concentration profile that proposes to minimize the dose-related side-effects of the drug while maintaining the efficacy within the therapeutic index.

Tizanidine is a centrally acting alpha$_2$-adrenergic agonist. Its chemical name is 5-chloro-4-(2-imidazolidinyl-2-ylamino)-2-1, 3-benzothiadiazole. Tizanidine's molecular formula is $C_9H_8ClN_5S$ and molecular weight is 290.2.

Tizanidine hydrochloride is available in the form of 2, 4 and 6 mg capsules and as 2mg and 4mg tablets for oral administration in the trade name of Zanaflex®. It is also available in the form of 2 and 4 mg tablets for oral administration in the trade name of Sirdalud™. It acts as a potent central muscle relaxant in the treatment of painful muscle spasms associated with spinal disorders and after surgery and also in certain arthritic conditions.

There are several ways of achieving controlled release of active substances. It may be achieved by a controlled release coating, embedding the drug in a controlled release matrix or a combination thereof.

Suitable controlled release coatings include water-insoluble waxes or polymers such as acrylic resins - preferably poly(meth)acrylates, or water-insoluble celluloses - preferably ethyl cellulose. In order to regulate the rate of release of the active substance, the controlled release coatings may also contain, in addition to the water-insoluble polymers, water-soluble polymers which act as channeling agents, such as polyvinylpyrrolidone or water-soluble celluloses, preferably hydroxypropyl methylcellulose or hydroxypropylcellulose,

and/or hydrophilic pore formers, such as sucrose, sodium chloride or mannitol and/or known plasticizers.

For the purposes of controlled release, the active substances may also be present in a controlled release matrix. Preferably the active substance will be uniformly distributed in the matrix. Physiologically compatible, hydrophilic materials, which are known to persons skilled in the art, may be used as matrix materials. Hydrophilic matrix materials which are used are polymers, preferably cellulose ethers, cellulose esters and/or acrylic resins. Especially preferred matrix materials include ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, such as the salts, amides or esters.

Hydrophobic materials, such as hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or ethers or mixtures thereof can also be used as matrix materials.

It is also possible to use mixtures of the stated hydrophilic and hydrophobic materials as a controlled release matrix material.

In a preferred embodiment, the present invention comprises an oral extended release dosage form of tizanidine in which the drug is uniformly dispersed in a matrix comprising of hydroxypropyl methyl cellulose and partially or fully pregelatinised starch.

Several factors affect the rate of drug release from an extended release polymeric matrix. The physicochemical characteristics of the drug such as degree of water solubility, molecular weight and the diffusion coefficient from the hydrated matrix play a very important role in determining the mechanism of drug release. Also, physicochemical characteristics of the diluents added to the matrix affect the rate of drug release.

Tablet excipients as per the present invention comprises:

1. Diluents, as herein described

2. Retardants as herein described
3. Lubricants as herein described

Diluents according to the present invention are inert materials needed to be added to the active ingredient to make them more acceptable. Diluents are fillers designed to make up the required bulk of the tablet when the drug dosage itself is inadequate to produce this bulk. Tablet formulations may contain diluents for secondary reasons: to provide better tablet properties such as improved cohesion, to permit use of direct compression manufacturing, or to promote flow.

Lactose is the most widely used diluent in tablet formulation. Lactose is an excipient that has no reaction with most drugs, whether it is used in the hydrous or anhydrous form. Anhydrous lactose has the advantage over lactose in that it does not undergo the Maillard reaction, which can lead to browning and discoloration with certain drugs. Lactose formulations show good drug release rates, their granulations are readily dried and the tablet disintegration times of lactose tablets are not strongly sensitive to variations in tablet hardness. Lactose is a low cost diluent. Usually fine grades of lactose are used in the preparation of tablets since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently. Generally, the grade of lactose chosen is dependent on the type of dosage form being developed. Direct-compression grades are often used to carry small quantities of drug and this permits tablets to be made without granulating.

Direct-compression grades of lactose are more fluid and more compressible than crystalline or powdered lactose and generally composed of spray-dried lactoses which contain specially prepared pure alpha lactose monohydrate along with a small amount of amorphous lactose. The amorphous lactose improves the compression force/hardness profile of the lactose. Other specially produced direct-compression grades of lactose do not contain amorphous material but may contain glassy or vitreous areas which impart improved compressibility. The use of direct-compression grades of lactose results in tablets

of higher breaking strength than standard lactose. Concentrations of lactose generally used in these formulations are from 65-85%.

Microcrystalline cellulose, (Avicel®-Manufacturer- FMC Corp.) according to the present invention is a direct compression material. It is the most compactable material available for pharmaceutical use. The flow properties of the material are generally good, and the direct compression characteristics are excellent. This is a somewhat unique diluent in that while producing cohesive compacts, the material also acts as a disintegrating agent. Due to the self disintegrating property of Avicel it requires little lubricant. Microcrystalline cellulose is often added to tablet formulation for several possible functions. It is a commonly employed excipient. The present invention employs Avicel pH-102 in the concentration of 20-90%. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant properties.

Anhydrous dibasic calcium phosphate is used in pharmaceutical products because of its compaction properties, and the good-flow properties of the coarse grade material. The predominant deformation mechanism of anhydrous dibasic calcium phosphate coarse-grade is brittle fracture and this reduces the strain sensitivity of the material, thus allowing easier transition from the laboratory to production scale. Anhydrous dibasic calcium phosphate is abrasive and a lubricant is required for tabletting, for example 1% magnesium stearate or 1 % sodium stearyl fumarate. Two particle size grades of anhydrous dibasic calcium phosphate are used in the pharmaceutical industry. Milled material is typically used in wet-granulated or roller-compacted formulations. The unmilled or coarse-grade material is typically used in direct-compression formulations. Anhydrous dibasic calcium phosphate is non-hygroscopic and stable at room temperature. It does not hydrate to form the dihydrate.

Pregelatinised starch (Starch 1500® -Manufacturer- Colorcon) according to the present invention influences the drug release from hydroxypropyl methylcellulose (HPMC) sustained release matrix formulations. Use of Starch 1500 significantly reduces the drug release as compared to formulations containing MCC or lactose. Starch 1500 is not an inert filler in HPMC matrices, but it actively contributes to the mechanism of drug release

causing a decrease in drug release rate. Increasing concentrations of Starch 1500® (20, 35 and 49.25% w/w) in the formulations caused a decrease in their release profiles. Drug release from matrices containing Starch 1500® was slower than when lactose or MCC was used.

Retardants control the release of an active substance from a tablet matrix. As mentioned above, retardation of drug release may be achieved either by a controlled release coating or by embedding the drug in a controlled release matrix of a hydrophilic or hydrophobic polymer or a combination thereof.

Eudragit RSPO and Eudragit NE 30D (Manufacturer-BASF) belong to the class of methacrylic acid copolymer namely polymethacrylates. Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethylmethacrylates, methacrylic acid and methacrylic acid esters in varying ratios. They are anionic in character, based on methacrylic acid and methyl methacrylate, for example having a ratio of free carboxyl groups; methyl-esterified carboxyl groups of 1:>3, e.g. around 1:1 or 1:2, and with a mean molecular weight of 1,35,000. They have solubility in aqueous media at pH 5.5. Such polymers may be used either alone or with a plasticizer. They are used to form water-insoluble film coats for sustained release products.

Eudragit RS PO is a fine white powder with a slight amine-like odor.It is characteristically the same polymer as Eudragit RL and RS. It contains > 97% of dry polymer.

Eudragit NE 30 D is an aqueous dispersion of a neutral copolymer consisting of polymethacrylic acid esters. The dispersions are milky-white liquids of low viscosity and have a weak aromatic odor. Films prepared from the lacquer swell in water, to which they become permeable. Thus, films produced are in-soluble in water, but give pH-independent drug release.

Polymethacrylate copolymers are widely used as film-coating materials in oral pharmaceutical formulations. Larger quantities (5-20%) of dry polymer are used to control

the release of an active substance from a tablet matrix (Handbook of Pharmaceutical Excipients Third Edition). They are generally regarded as nontoxic and nonirritant materials. A daily intake of 2mg/kg body weight of Eudragit (equivalent to approximately 150 mg for an average adult) may be regarded as essentially safe in humans. (Handbook of Pharmaceutical Excipients Third Edition).

Ethyl cellulose dispersion (Surelease® -Manufacturer- Colorcon) is a unique combination of film-forming polymer, plasticizer and stabilizers. Designed for sustained release and taste masking applications, Surelease is an easy to use, totally aqueous coating system using ethyl cellulose as the release rate controlling polymer. The dispersion provides the flexibility to adjust drug release rates with reproducible profiles that are relatively insensitive to pH. The principal means of drug release is by diffusion through the ethyl cellulose membrane and is directly controlled by film thickness. Increasing or decreasing the quantity of Surelease applied can easily modify the rate of release. Usually, ethyl cellulose is used in the form of sustained release coating in the concentration of 3-20% (Handbook of Pharmaceutical Excipients-Third Edition). But it may also be used as a filler in the matrix to sustain drug release. With Surelease dispersion, reproducible drug release profiles are consistent right through development to scale-up and production processes. It's benefits are that it is a totally aqueous system and a ready plasticized formulation. It gives consistent, uniform drug release independent of pH. The release rates produced are reproducible through scale-up.

Polyethylene oxide polymers (Polyox® WSR 301 -Manufacturer- Dow) according to the present invention are non-ionic, high molecular weight water-soluble polymers. Molecular weights range from 100,000 to about 8,000,000. They meet the requirements of the Food Chemicals Codex, the International Codex Alimentarius and US Pharmacopoeia (USP) or National Formulary (NF). They are white, free-flowing hydrophilic powders with a long history of successful applications in pharmaceutical products, in uses such as controlled release solid dose matrix systems. The higher molecular weight grades provide delayed drug release via the hydrophilic matrix approach. Polyox® resins are used as controlled release solid dose matrix systems in the concentrations of 1-5%. (Handbook of

Pharmaceutical Excipients-Third Edition). Polyox® resins are very versatile polymers for controlled release applications. Upon exposure to water or gastric juices, they hydrate and swell rapidly to form hydrogels with properties ideally suited for controlled drug-delivery vehicles. Because Polyox® resins are nonionic; no interaction between drug and polymers is to be expected.

In a preferred embodiment of the invention, retardants are selected from the group of hydroxypropyl methylcelluloses (HPMC) like HPMC K15M, HPMC K100M, HPMC K100M CR (Methocel®, Manufacturer - Colorcon). Primary control of drug release is achieved by the Methocel content, varying the ratio of drug to polymer. As the proportion of hydroxypropyl methylcellulose increases, the release rate is reduced. In the case of less water soluble drugs viscosity type offers a secondary control mechanism.

Hydroxypropyl methylcellulose is a very versatile material for the formulation of soluble matrix tablets. HPMC is a widely accepted pharmaceutical excipient and is available in a wide range of molecular weights; effective control of gel viscosity is easily provided. Hydroxypropyl methylcellulose is primarily used as a tablet binder in film coating and as an extended release tablet matrix. Concentrations of between 2-5% w/w may be used as a binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of drugs from a matrix at levels 10-80% w/w in tablets.

Lubricants reduce friction by interposing a film of low shear strength between the tablet mass and the confining die wall interface during tablet formation and ejection.They also play the role of anti-adherents wherein they prevent sticking to surfaces like the faces of tablet punches. Lubricants also act as glidants thereby improving the flow by modifying the interaction between particles. Therefore the concept of a lubricant system is generally the use of two substances to maximize overall lubricant effect in all three areas as lubricant, antiadherent and glidant. For example combining magnesium stearate with colloidal silica.

Colloidal silicon dioxide (Aerosil®- Manufacturer- Degussa) according to the present invention is widely used in pharmaceuticals especially in tablets as a glidant. Aerosil acts as

a glidant in the concentration of 0.1-0.5% (Handbook of Pharmaceutical Excipients-Third Edition). Its small particle size and large specific surface area give it desirable flow characteristics which are exploited to improve the flow properties of dry powders in tabletting.

Stearic acid according to the present invention acts as a tablet lubricant. Stearic acid acts as a lubricant in the concentration of 1-3% (Handbook of Pharmaceutical Excipients-Third Edition).

In one aspect, the invention provides a solid dosage form comprising tizanidine HCl in a sustained release matrix and a COX-II inhibitor, valdecoxib, as an immediate release component in the said dosage form.

Valdecoxib belongs to a class of nonsteroidal anti-inflammatory medications (NSAIDs) called COX-2 inhibitors. Valdecoxib is available in the form of 10 and 20 mg oral, immediate release film-coated tablets by the trade name BEXTRA® (Pharmacia-Pfizer). Valdecoxib is chemically designated as 4-(5-methyl-3-phenyl-4-isoxazolyl) benzene sulfonamide. Its molecular weight is 314.36 & empirical formula is C16H14N2O3S. It is a second generation COX-2 inhibitor for the treatment of rheumatoid arthritis. The COX-2 enzyme plays a role in causing arthritis pain and inflammation. Valdecoxib works by targeting the action of the COX-2 enzyme to relieve the pain, stiffness and inflammation associated with arthritis.

The invention is further disclosed and detailed in the following examples, which are not to be taken as limiting:

Example 1

Table 1

Sr. no.	Ingredient	Quantity/tab (mg)	%w/w
1	Tizanidine HCl	6.864	2.29
2	Starch 1500	141.04	47.01
3	HPMC K100M CR	150	50.00
4	Colloidal SiO2	0.6	0.20
5	Stearic acid	1.5	0.50
	Average Tablet Weight (mg)	300	

This example demonstrates a preferred method and composition.

All ingredients except stearic acid are sifted through mesh # 30. The ingredients are blended together by Geometric Dilution and mixed thoroughly in a double-cone blender and then lubricated with stearic acid that is previously passed through mesh # 60. The blend is directly compressed into tablets having target weight of 300 mg.

In Vitro Dissolution Profile

The tablets were tested in VanKel dissolution bath (USP apparatus 2, 50 rpm) at 37°C in 500 ml of 0.01(N) HCl for 16 hours. The tizanidine in the samples was determined by an HPLC system on a C-18 column using an aqueous buffer pH 7.4: methanol with UV detection at 230 nm. The results obtained are shown in Figure 1.

Table 2

Dissolution profile

Time (hours)	% tizanidine release
0	0
1	20
3	39
4.5	50
6	59
8	69
10	76
14	88
16	93

Example 2

Table 3

Sr. no.	Ingredient	Quantity/tab (mg)	%w/w
1	Tizanidine HCl	6.864	2.29
2	Lactose, anhydrous	40.64	13.55
3	Starch 1500	61	20.33
4	HPMC K100M CR	150	50.00
5	Eudragit NE 30D	134 (40)	13.33
6	Stearic acid	1.5	0.50
	Average Tablet Weight (mg)	300	

All ingredients 1 to 4 are sifted through mesh # 30 and mixed in a planetary mixer. The blend is then granulated using Eudragit NE 30D dispersion (134 g of the dispersion contains 40g of total solid content). These granules are dried to obtain a loss-on-drying (LOD) value below 2% and then milled. The granules are then passed through mesh # 20

and lubricated with stearic acid in a double-cone blender. The blend is compressed into tablets having target weight of 300 mg.

Table 4

Dissolution profile

Time (hours)	% tizanidine release
0	0
1	21
3	42
4.5	52
6	60
8	69
10	76
14	85
16	89

Example 3

Table 5

Sr. no.	Ingredient	Quantity/tab (mg)	%w/w
1	Tizanidine HCl	6.864	2.29
2	Lactose, anhydrous	30	10.00
3	Starch 1500	81.04	27.01
4	HPMC K100M CR	180	60.00
5	Colloidal SiO2	0.6	0.20
6	Stearic acid	1.5	0.50
	Average Tablet Weight (mg)	300	

All ingredients except stearic acid are sifted through mesh # 30, mixed thoroughly in a double-cone blender and then lubricated with stearic acid that is previously passed through mesh # 60. The blend is directly compressed into tablets having target weight of 300 mg.

Table 6

Dissolution profile

Time (hours)	% tizanidine release
0	0
1	22
3	42
4.5	54
6	63
8	74
10	82
14	94
16	99

Example 4

Table 7

Sr. no.	Ingredient	Quantity/tab (mg)	%w/w
1	Tizanidine HCl	6.864	2.29
2	Starch 1500	81.04	27.01
3	HPMC K100M CR	150	50.00
4	Ethyl cellulose STD FP 100 (Ethocel)	60	20.00
5	Colloidal SiO2	0.6	0.20
6	Stearic acid	1.5	0.50
	Average Tablet Weight (mg)	300	

Tizanidine HCl and 5%w/w of Ethocel are sieved through mesh # 40 and dissolved with stirring in ethanol 95%. It gives a slightly gel-like mass. The remaining amount of Ethocel is taken in a planetary mixer along with starch 1500 and 30%w/w of HPMC K100M. It is

dry-mixed for 5 minutes and then granulated with the gel-like mass of drug and Ethocel obtained earlier. These granules are dried to get a loss-on-drying value below 2%, then milled and passed through mesh # 30. These granules are blended with the remaining (20% w/w) of HPMC K100M and colloidal SiO2 in a double-cone blender and then lubricated with stearic acid that is previously passed through mesh # 60. The final blend is compressed into tablets having target weight of 300 mg.

Table 8

Dissolution profile

Time (hours)	% tizanidine release
0	0
1	14
3	30
4.5	38
6	45
8	53
10	60
14	69
16	74

Optionally, these tablets may then be coated with an immediate-release coating of valdecoxib or can be formulated into bilayer tablets containing one layer of tizanidine in sustained release matrix and a second immediate-release layer of valdecoxib. The following examples are given.

Example 5

Immediate-release coating of Valdecoxib:

The composition and method for the drug coating is as follows:

Valdecoxib: Opadry® (RTM of Colorcon) (Colored): PEG 8000 in a proportion of 2:1: 0.5 dispersed uniformly in Methylene Dichloride: Isopropyl alcohol (40:60) solvent mixture. This dispersion is sprayed onto the tablets such that there is 20 mg Valdecoxib in the final weight gain by each tablet.

Example 6

Immediate-Release layer of Valdecoxib:

The following composition can be used to formulate Valdecoxib as immediate-release granules that can be compressed with the final blend of tizanidine hydrochloride to give bilayer tablets. Conventional method of wet granulation using water is used to formulate these granules.

Table 9

Sr. no.	Ingredient	Quantity/tab (mg)
1	Valdecoxib	20
2	Lactose monohydrate	38.25
3	Microcrystalline cellulose	27
4	Pregel starch	5
5	PEG 8000	4
6	Croscarmellose sodium	5
7	FDC Yellow no. 6 (Sunset Yellow)	0.5
8	Magnesium stearate	0.25
	Average weight of Layer (mg)	100

EXAMPLE 7

Human PK Study of Tizanidine HCl Extended Release & Valdecoxib IR Tablets

A product of the present invention comprising Tizanidine 6mg Extended Release formulation (as per Example 1) and Valdecoxib 20mg Immediate Release formulation (as

per Example 6) has been studied for human bioavailability in ten healthy human subjects in an open label, crossover design comparing with Tizanidine 2mg IR tablets(Glenmark Pharmaceuticals) t.i.d. and Valdecoxib 20mg IR tablets (Bextra ®) of Pharmacia-Pfizer.

Tizanidine Extended Release formulation has shown relative bioavailability of 63% (as reflected by AUC $_{(0-\infty)}$, Area Under Plasma Concentration vs. time curve) with sustained levels of drug appearing up to 24 hours. A shift in peak time from 1.40 hours (for IR product) to 4.10 hours (for Extended Release product) and a two hour extension in half-life with respect to IR product were supportive of sustained drug release from the product of present invention without any signs of dose dumping. In addition the extended Release formulation has shown MRT (Mean Residence Time) of 8.89 hours vs. 2.84 hours of IR product reflecting the continuous presence of active drug levels during the dosage period.

Table 10

Summary PK of Tizanidine (n=10)

		Mean Data		
Parameter	Units	Reference (IR Product)	Test (Extended-Release Formulation)	Ratio (%)
C_{max}	ng/ml	5.45	3.28	60.18
C^{∞}_{avg}	ng/ml	1.06	1.40	132.08
$AUC_{(0-t)}$	ng.hr/ml	41.25	24.85	60.24
$AUC_{(0-\infty)}$	ng.hr/ml	42.95	26.79	62.37
$t_{1/2}$	hr	2.25	4.15	184.44
T_{max}	hr	1.40	4.10	292.86

Considered the above single day data for both IR & Extended Release formulations, the predicted PK parameters at doses given for 5 day chronic treatment (i.e., for IR formulation the dose design is 2mg t.i.d. for 5 days and for Extended Release formulation the dose

design is 6mg o.d. for 5 days) are tabulated below. The Extended Release formulation is found to be 100% equivalent with respect to the IR product.

Table 11

Predicted Summary PK of Tizanidine (n=10) after 5 day chronic treatment

		Mean Data		
Parameter	Units	Reference (IR Product)	Test (Extended-Release Formulation)	Ratio (%)
C^{∞}_{avg}	ng/ml	1.06	1.08	101.89
$AUC_{(0-t)}$	ng.hr/ml	130.51	128.29	98.30
$AUC_{(0-\infty)}$	ng.hr/ml	130.73	129.49	99.05
$t_{1/2}$	hr	2.25	4.15	184.14
MRT	hr	2.84	8.89	313.03

The Valdecoxib IR formulation was found to be bio-equivalent with respect to (Bextra ®) of Pharmacia-Pfizer as per USFDA guidelines.

Table 12

SUMMARY STATISTICAL EVALUATIONS OF PHARMACOKINETIC PARAMETERS OFVALDECOXIB

UNTRANSFORMED DATA

PARAMETER	UNITS	LEAST SQUARE MEANS Reference (Glenmark Formulation)	Test (Bextra®)	RATIO(%)	% intra CV	90 % CONFIDENCE INTERVALS Lower	Upper
C_{max}	(µg.hr/ml)	0.451	0.415	92.13	10.35	*84.27*	*100.00*
$AUC_{(0-t)}$	(µg.hr/ml)	6.497	6.368	98.02	8.67	*92.24*	*103.81*
$AUC_{(0-\infty)}$	(µg.hr/ml)	7.516	7.340	97.66	9.33	*91.50*	*103.82*
$t_{1/2}$	(hr)	10.926	11.331	103.71		*97.12*	*110.29*
T_{max}	(hr)	3.899	3.964	101.68		*86.40*	*116.96*

LN-TRANSFORMED DATA

PARAMETER	UNITS	LEAST SQUARE MEANS		RATIO(%)	% intra CV	90 % CONFIDENCE INTERVALS	
		Reference	Test			Lower	Upper
C_{max}	(µg.hr/ml)	0.440	0.412	93.60	11.58	*86.15*	*101.69*
$AUC_{(0-t)}$	(µg.hr/ml)	6.404	6.296	98.32	8.92	*92.70*	*104.28*
$AUC_{(0-\infty)}$	(µg.hr/ml)	7.404	7.219	97.50	9.61	*91.59*	*103.80*
$t_{1/2}$	(hr)	10.660	11.128	104.38		*96.92*	*112.42*
T_{max}	(hr)	3.795	3.877	102.15		*88.97*	*117.30*

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